PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of

Peter HAWKINS et al.

Group Art Unit: 1641

Application No.: 09/816,225

Examiner: P. Do

Filed: March 26, 2001

Docket No.: 109068

For: MAGNETIC PARTICLE DETECTION

## REQUEST FOR RECONSIDERATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In reply to the April 5, 2005 Office Action, the period for reply being extended by a Petition for Extension of Time filed herewith, and in consideration of the July 26, 2005 personal interview with the Examiners, reconsideration of the application is respectfully requested in light of the following remarks.

Claims 9-13 are pending in this application. Applicants appreciate the courtesies shown to Applicants' representative by Examiners Do and Le during the July 26 personal interview. Applicants' separate record of the summary of the substance of that interview is contained in the following remarks.

The Office Action, on page 2, indicates that the rejection under 35 U.S.C. §102 from the previous Office Action is withdrawn; and states, on page 5, that claims 9-13 are "free of prior arts." The Office Action, on pages 2-5, for the first time, rejects claims 9-13 under 35 U.S.C. §112, first paragraph, asserting that the disclosure is not enabling and/or that the

claims fail to comply with the enablement requirement. These rejections are respectfully traversed.

The Office Action, on page 2, states that "[a] function group or a binder conjugated to magnetic particles in step (b) of claim 1 is critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure." Specifically, the Office Action indicates that Applicants' disclosure on page 6, lines 5-10, discloses that the magnetic particles are bound to second molecules which bind with the layer of molecules on a substrate so as to bind the magnetic particles to the substrate, and indicates that the second molecules are not recited in claim 1, which Applicants interpret to mean independent claim 9. The Office Action goes on to assert that "(t)hese second molecules are critical to the present invention because they bind covalently to the monolayer of molecules on the substrate as to capture the magnetic labels. Covalent interaction is a stable binding interaction. Thus, the magnetic particles bind to the molecules on the substrate through the second molecules would be stably captured on the substrate." These assertions are incorrect.

A. **"Second Molecules" Are Not Critical**

Applicants' disclosure, at page 6, lines 5-11, indicates that typically magnetic particles are bound to a respective number of second molecules and a reaction binds the second molecules with the monolayer of molecules on the substrate. This paragraph goes on to state that "[a]lternatively however, the magnetic particles may be designed to react directly with the molecules bound to the substrate." Therefore, the second molecules are not required. As such, the Office Action's assertion that second molecules are required in claim 9 is clearly in error. MPEP §2164.08(c) instructs that "[I]n determining whether an unclaimed feature is critical, the entire disclosure must be considered. Features which are merely preferred are not to be considered critical." *In re Goffe*, 542 F.2d 567, 191 USPQ 429, 431 (CCPA 1976). In this case, while employing second molecules may be "typical," there is disclosed an

alternative direct reaction with the molecules bound to the substrate. Therefore, second molecules clearly are not "critical" or "essential"

**B. No Undue Experimentation Is Required**

MPEP §2164.01, quoting *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), states "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation" (emphasis added). The MPEP continues "A patent need not teach, and preferably omits, what is well known in the art." *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984) (emphasis added).

The Office Action sets forth and analyzes the enumerated factors, drawn from MPEP§2164.01(a), that are to be considered, as a whole, when determining that experimentation may be undue on pages 3-5 of the Office Action. Specifically, the Office Action, at the top of page 4, asserts that the prior art fails to teach a method of binding the magnetic particles (non-bound) as labels to molecules of the substrate. This assertion is incorrect. As such, the rest of the analysis regarding a level of experimentation to arrive at what was known necessarily fails.

In support of Applicants' conclusions that the above statements are incorrect, Applicants respectfully submit the enclosed references which indicate, among other facts, that it was known to those skilled in the art in 1977 and in 1980 that: (1) a magnetic particle can bind directly to a molecule such as an antibody based on the use of for example Gadolinium as a probe in the Fc region of a homogeneous … antibody; and (2) in addition to covalent

bonding to the monolayer of the substrate, which the Office Action indicates is "critical," other binding reactions are possible including, for example, electrostatic bonding as is indicated by the attached discussion of colloidal gold bonding to a protein. These references indicate that the state of the prior art as early as 1977 included methods of binding magnetic particles as labels directly to molecules of a substrate. As such, no undue experimentation would have been required. Therefore, the disclosure cannot be considered non-enabling as to this feature, contrary to what is asserted by the Office Action.

Incidentally, Applicants respectfully note the Office Action's recognition that "the level of skill in the art is high," thereby further undercutting the conclusion that "undue" experimentation would have been required.

* * *

For at least the above-stated reasons, Applicants assert that (1) the Office Action is in error; and (2) the disclosure meets the written description and enablement requirements of 35 U.S.C. §112, first paragraph.

Applicants' representative presented the above arguments regarding the allowability of claims 9-13 to Examiners Do and Le during the July 26 personal interview. Specifically, all of the §112, first paragraph, issues, and evidence to overcome the erroneous assertions in the Office Action were discussed. The Examiners did not rebut any of the arguments presented by Applicants' representative. The Examiners indicated that a close reconsideration will be taken when Applicants submit a formal response.

In view of the foregoing, Applicants respectfully submit that this application is in condition for allowance. Favorable reconsideration and prompt allowance of claims 9-13 are earnestly solicited.

Should the Examiner believe that anything further would be desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned representative at the telephone number set forth below.

Respectfully submitted,

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Registration No. 27,075

Daniel A. Tanner, III
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JAO:DAT

Attachments:

Petition for Extension of Time
Excerpt from Willan et al., *The use of gadolinium as a probe in the Fc region of a Homogeneous anti-(type-III pneumococcal polysaccharide) antibody*, 151 Biochem. J. 205-11 (1977)
Excerpt from Jessen et al., *Selective binding of colloidal gold-protein conjugates epidermal phosphorous-rich keratohyaline granules and cornified cells*, 87 J. Invest. Dermatol. 737-40 (December 1986)
Excerpt from Goodman et al., *A review of the colloidal gold marker system*, Scan Electron Microsc. 133-46 (1980)

Date: August 4, 2005

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Biochem. J. (1977) 161 (205–211) (Printed in Great Britain)

# The use of gadolinium as a probe in the Fc region of a homogeneous anti-(type-III pneumococcal polysaccharide) antibody.

Willan KJ, Wallace KH, Jaton JC, Dwek RA

The binding of gadolinium [Gd(III)] to a homogeneous rabbit anti-(type-III pneumococcal polysaccharide) IgG (immunoglobulin G) and its Fab (N-terminal half of heavy and light chain) and Fc (C-terminal half of heavy-chain dimer) fragments was demonstrated by measurements of solvent-water proton relaxation rates in the appropriate Gd(III) solutions. At pH 5.5 the binding of Gd(III) to the Fc fragment is much tighter (KD approx. 5 micronM) than binding to the Fab fragment (KD approx. 250 micronM). The binding of Gd(III) to the whole IgG molecule (KD approx. 4 micronM) is very similar to that for the Fc fragment alone. This specificity of binding to the Fc region allows the use of Gd(III) as a probe of the Fc conformation. The environment of the Gd(III) in the Fc region of whole IgG is not affected by the presence of octasaccharide derived by hydrolysis of type-III pneumococcal polysaccharide, but the corresponding 28-unit saccharide does cause detectable changes. The addition of 16-unit saccharide to anti-(SIII polysaccharide) IgG in the presence of Gd(III) does not change the solvent water proton relaxation rate, although aggregation does occur. The effects of the 28-unit saccharide may be explained therefore by a change in the tumbling time of the IgG. From a study of the effect of various antigen/antibody ratios, it is concluded that the 28-unit-saccharide-induced changes in the Gd(III) environment in the Fc region are caused by the specific geometrical structure of the antigen-antibody complexes formed, and not simply by occupancy of the combining sites on the antibody.

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1: J Invest Dermatol. 1986 Dec;87(6):737-40. Related Articles, Link

# Selective binding of colloidal gold-protein conjugates to epidermal phosphorus-rich keratohyaline granules and cornified cells.

Jessen H, Behnke O.

Colloidal gold solutions conjugated with staphylococcal protein A (SpA) are widely used in high-resolution immunocytochemical studies to visualize antibodies bound at antigenic sites. Here we report that colloidal gold solutions conjugated with SpA, bovine serum albumin (BSA), or gelatin bind selectively to structures in glutaraldehyde-fixed, plastic-embedded epidermis of rabbit, mouse, and human. Two types of keratohyaline granules are present in epidermis, a phosphorus-rich (PR) and a sulphur-rich (SR) type. The PR keratohyaline granules were strongly labeled with gold particles, whereas SR keratohyaline granules or other structures in the living cells of epidermis were unlabeled. The PR keratohyaline granules are assumed to be precursors of the matrix protein of cornified cells, and intense gold labeling occurred over the lower layer of cornified cells (i.e., stratum lucidum). More superficial cornified cells were weakly labeled or unlabeled. The gold labeling pattern was identical whether SpA, BSA, or gelatin was used to stabilize the colloidal gold solution. The mechanism of binding of protein-conjugated gold to PR keratohyaline granules and matrix protein of cornified cells is not clear. It is speculated that the charged gold particles are not completely coated by the stabilizing protein, allowing for an electrostatic interaction with charged proteins in sections of cells.

PMID: 2431071 [PubMed - indexed for MEDLINE]

1: Scan Electron Microsc. 1980;(Pt 2):133-46.

Related Articles, Lir

# A review of the colloidal gold marker system.

Goodman SL, Hodges GM, Livingston DC.

Colloidal gold can be used as a particulate marker for the detection and localization of target molecules by various modes of microscopy (light and fluorescent microscopy, scanning and transmission electron microscopy) using both direct and indirect labeling approaches. Several techniques are available for the preparation of gold markers in a siz range of 5nm to 150nm, their mean size and shape characteristics and absorption spectr varying with particle size. Under appropriate conditions, colloidal gold will bind macromolecules by non-covalent electrostatic adsorption with little change in the specifi activity of the bound macromolecule. This interaction is influenced by a number of factors including ionic concentration, pH conditions (in correlation with the protein pI values) and protein stabilizing levels. Presence of reactive protein on probes can be demonstrated and quantitated by direct and indirect radioactive binding assays and agglutination assays. These assays provide convenient procedures for characterizing stability, and behaviour in storage, of gold probes. Stability of gold probes under conditions where competing proteins are present, under freeze-thaw cycles and under SEM preparation conditions have been evaluated in this paper. Some of the basic procedures in the application of gold probes to cell labeling are briefly discussed togethe with certain limitations of the colloidal gold marker system. A bibliography of gold prob cell labeling studies is included.

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